Web-appendix

Web-appendix 1a. Risk categories for clinical trials with investigational medicinal products according to draft Clinical Trial Ordinance compared to EU-Regulation and other initiatives

	Category A	Category B	Category C
[1] Draft Clinical Trials Ordinance	IMPs approved in Switzerland, if: a) Administration (galenic form, dosage and indication) complies with specification in summary product characteristics (SPC), or b) if administration deviates from SPC specification but fulfils the following criteria: 1) indication lies within the same disease group, defined by the three digit code corresponding to the International Classification of Diseases (ICD), 2) the severity of the disease/condition is equivalent or lower than that specified in the SPC, 3) the dosage, in case of self-limiting disease, is the same or lower than that specified in the SPC.	Trials that involve IMPs approved in Switzerland, if: a) Administration deviates from SPC specifications and one or more of the criteria listed above are not fulfilled.	Trials that involve IMPs not yet approved in Switzerland.
[2] OECD	Category A: Clinical trials on authorized medicinal products (according to national or regional regulations) tested in accordance with their marketing authorization.	Category B: concerns clinical trials on authorized medicinal products tested according to treatment regimens outside their marketing authorization (in terms of population, condition, administration, or dosage): 1. supported by published evidence or guidance or established medical practice; 2. not supported by published evidence or guidance or established medical practice	Category C: concerns clinical trials on medicinal products without any marketing authorization
[3] UK MHRA	Type A (no higher than that of standard medical care): Trials involving medicinal products licensed in any EU Member State if: • they relate to the licensed range of indications, dosage and form or, • they involve off-label use (such as in paediatrics and in oncology etc) if this off-label use is established practice and supported by sufficient published evidence and/or guidelines	Type B (somewhat higher than that of standard medical care): Trials involving medicinal products licensed in any EU Member State if: • such products are used for a new indication (different patient population/disease group) • or substantial dosage modifications are made for the licensed indication • or if they are used in combinations for which interactions are suspected • Trials involving medicinal products not licensed in any EU Member State if: • the active substance is part of a medicinal product licensed in the EU (A grading of TYPE A may be justified if there is extensive clinical experience with the product and no reason to suspect a different safety profile in the trial population)	Type C (markedly higher than that of standard medical care)
EU –Regulation	'Low-intervention clinical trial' means a clinical trial which fulfils all of the following conditions: (a) the investigational medicinal products, excluding placebos, are authorized; (b) according to the protocol of the clinical trial, (i)the investigational medicinal products are used in accordance with the terms of the marketing authorization; or (ii) the use of the investigational medicinal products is evidence-based and supported by published scientific evidence on the safety and efficacy of those investigational medicinal products in any of the Member States concerned; and (c) the additional diagnostic or monitoring procedures do not pose more than minimal additional risk or burden to the safety of the subjects compared to normal clinical practice in any Member State concerned.		Clinical trials that are not low-intervention clinical trials: (Clinical trials with non-authorized investigational medicinal products or placebos)

[1] The final version of the Clinical Trials Ordinance implemented in January 2014 included all the above listed criteria apart from the b-2 *"the severity of the disease/condition is equivalent or lower than that specified in the SPC"* [2] "These principles combine (A) a stratified approach, generally based on the marketing authorization status of the medical

product, that can be applied in legislation or regulation in a common manner across countries, with (B) a trial-specific approach that considers a large number of other issues such as additional diagnostic procedures, specific populations concerned, or informed consent.”; [3] Principles for risk assessment include: the risk to participant safety in relation to the investigational medicinal product, all other risks related to the design and methods of the trial (including risks to participants safety and rights, as well as reliability of results).

Web appendix 1b. Risk categories for clinical trials with medical devices and other interventions according to draft Clinical Trials Ordinance

Medical device	Category A Trials that involve MDs licensed in Switzerland, if: the intended use complies with the specifications of the CE-mark	Category C Trials that involve medical devices not licensed, banned or restricted in Switzerland
Non-pharmacological / Non-device intervention	Category A Trials that involve non pharmacological/non-device interventions, if: -the intervention is established as standard medical practice, or is -recommended in an international accepted treatment guideline	Category B Trials that involve non-pharmacological/non-device interventions if: - the intervention is neither established as standard medical practice, nor -recommended in an international accepted treatment guideline

Web-appendix 2. Forms used to develop the web-based questionnaire for the categorization of clinical trials with medicinal products, medical devices and non-pharmacological/non-device intervention using the concept approach

Risk based categorization according to concept
Clinical trials with medicinal products

ⓘ Instructions:

Thank you for participating in this pilot study. We ask you to complete this form as thoroughly as possible because it will help us to assess the practicability of the proposed risk categorization of clinical trials with medicinal products. The information provided will be treated strictly confidentially and will not have any implications whatsoever for your study already approved.

The risk categorization strategy proposes categorizing clinical trials with medicinal products into three categories (A, B or C), depending on the approval status of the investigational medicinal product and the intended use related to the approved indications (e.g. dosage and disease or condition's severity) as specified in the summary of product characteristics.

Please tick or complete the questions below according to the embedded instructions and indicate the resulting risk category of your study at the end of the questionnaire.

Please contact us pilot@admin.bag.ch *if you have any questions about completing this questionnaire.*

A. KEK number of your trial:

B. Please indicate the Ethics Committee you submitted your trial to?
[MCXX:Dropdown list with ECs?]

Approval status of investigational medicinal product (IMP)

1. Does the clinical trial evaluate IMP(s) approved in Switzerland by Swissmedic?
☐ Yes *(Please continue with question 2)*
☐ No →CATEGORY C

Administration of IMP

2. Does the IMP's administration (galenic form, dosage and indication) comply with the specifications in the summary of product characteristics (SPC)?
☐ Yes →CATEGORY A
☐ No *(Please continue with question 3)*

International classification of disease (ICD-10 Code)

3. Does the IMP's administration lie within the same disease group, as defined by the three digits ICD-10 code?
☐ Yes. Indicate the corresponding ICD-10 disease group code [_][_][_]
(Please, continue with question 4)
☐ No →CATEGORY B
☐ Not applicable (*Please indicate why and continue with question 4)*
a. ICD-10 does not include the disease

b. Disease cannot be clearly assigned to a 3-digits ICD-10 code
c. Other *(please specify)*:

Severity of disease or condition

4. Is the severity of disease/condition equivalent or lower than the severity specified in the SPC?

□ Yes *(Please, continue with question 5)*

□ No →CATEGORY B

□ Not applicable (*Please indicate why and continue with question 5)*

a. Disease cannot be clearly categorized into severity degrees
b. Severity of disease is not specified in the SPC
c. Other *(please specify)*:

Course of disease or condition

5. Is the disease or condition self-limiting (tends to end without treatment)?

□ Yes *(Please, continue with question 6)*

□ No *(Please, continue with question 7)*

Dosage of IMP by self-limiting disease or condition

6. In case of a self-limiting disease or condition, please indicate if the IMP dosage:

□ Lies within the therapeutic range as specified in the SPC →CATEGORY A

□ Is lower than specified in the SPC →CATEGORY A

□ Is higher than specified in the SPC →CATEGORY B

Dosage of IMP by NOT self-limiting disease or condition

7. In case the disease or condition is NOT self-limiting, please indicate if the IMP dosage:

□ Lies within the therapeutic range as specified in the SPC →CATEGORY A

□ Is lower than specified in the SPC →CATEGORY B

□ Is higher than specified in the SPC →CATEGORY B

Resulting risk category:

□ CATEGORY A

□ CATEGORY B

□ CATEGORY C

Risk based categorization according to concept
Clinical trials with medical devices

ⓘ Instructions:

Thank you for participating in this pilot study. We ask you to complete this form as thoroughly as possible because it will help us to assess the practicability of the proposed risk categorization of clinical trials with medical devices. The information provided will be treated strictly confidentially and will not have any implications whatsoever to your study already approved.

The risk categorization strategy proposes categorizing clinical trials with medical devices into two categories (A or C), depending on the approval status of the medical device and the intended use related to the approved indications as specified in the summary of product characteristics.

Please tick or complete the questions below, according to the embedded instructions and indicate the resulting risk category of your study at the end of the questionnaire.

Please contact us pilot@admin.bag.ch if you have any questions about completing this questionnaire.

C. KEK number of your trial:

D. Please indicate the Ethics Committee you submitted your trial to:
[Dropdown list with ECs]

Certification status of medical device (MD)

8. Does the clinical trial evaluate a CE marked medical device (MD)?

☐ Yes *(Please continue with question 2)*

☐ No →CATEGORY C

Restricted use in Switzerland

9. Is the use of the MD restricted or banned in Switzerland?

☐ Yes →CATEGORY C

☐ No *(Please continue with question 3)*

Administration of MD

10. Does the intended use of the MD comply with the certified range of indications specified in the CE-mark certification?

☐ Yes →CATEGORY A

☐ No →CATEGORY C

Resulting risk category:

☐ CATEGORY A

☐ CATEGORY C

Risk based categorization according to concept
Clinical trials with non-pharmacological interventions

ⓘ Instructions:

Thank you for participating in this pilot study. We ask you to complete this form as thoroughly as possible because it will help us to assess the practicability of the proposed risk categorization of clinical trials with non-pharmacological interventions. The information provided will be treated strictly confidentially and will not have any implications whatsoever to your study already approved.

The risk categorization strategy proposes categorizing clinical trials with non-pharmacological interventions into two categories (A or B), depending on the risk of the investigational health-related intervention compared to the standard treatment.

Please tick or complete the questions below according to the embedded instructions and indicate the resulting risk category of your study at the end of the questionnaire.

Please contact us pilot@admin.bag.ch if you have any questions about completing this questionnaire

E. KEK number of the trial:

F. Please indicate the Ethics Committee you submitted your trial to?
[MCXX: Dropdown list with ECs?]

Risk associated with the clinical trial intervention

The new legislation defines the risk associated with health-related intervention as minimal if Preventive, diagnostic, therapeutic, palliative or rehabilitative treatment for or involving persons; if they have no, or at most minor or temporary adverse psychological and/or physical effects on the participants

11. Please, indicate if the risk for the patient associated with the intervention you plan to evaluate in this trial, is minimal (as defined above).

☐ Yes *(please continue with question 2)*

Please indicate the key risks that you assessed as minimal

Type of risk *[Dropdown list]*	**Please describe** *[limited number of characters]*
Physical	
Psychological	
Other	

☐ No *(Please continue with question 2)*

Standard practice and guidelines

12. Is the trial intervention established as standard medical practice or recommended in an accepted treatment guideline?

☐ Yes

(Please provide the website link or PDF file of the published evidence or guideline you are referring to and continue with question 3)

☐ No → *CATEGORY B*

Use of investigational intervention (Indication and application) in the trial

13. Do the indication and the application of the investigational intervention comply with the standard medical practice or the recommendations of the indicated treatment guideline?

□ Yes (*Please, continue with question 5*)

□ No *(Please, continue with question 4)*

14. Please, indicate how does the application of the trial intervention differ from standard medical practice or recommendation in treatment guideline:

□ Minimal deviation (*Please, continue with question 5*)

□ Large deviation →CATEGORY B

Potentially harmful

15. Is the intervention you plan to evaluate in this trial, mentioned in the literature as potentially harmful?

□ Yes. → CATEGORY B

□ No → CATEGORY A

Resulting risk category:

□ CATEGORY A

□ CATEGORY B

Web-appendix 3. Ad-hoc categorization procedure. Set of regulatory requirements that correspond to each category by type of intervention (drug, medical devices or non-pharmacological/device interventions)

	Regulatory requirements for
Category A	**Clinical trials with investigational medicinal products (IMP)** - Only approval by ethics committee required (no Swissmedic approval required) - No mandatory trial specific insurance, but damages must be covered up to a maximum of CHF 3 million; reduced damage coverage (indemnification) up to a maximum of CHF 3 million - Rules on IMP management: no trial specific IMP management required, including IMP labelling and accountability. - Content of application dossier for IMP documentation: summary of product characteristics (no investigators brochure required); copy of manufacturer's general GMP documentation - Safety reporting: no documentation of adverse events (AEs) required; serious AEs (SAEs) with fatal outcome must be reported to the ethics committee only if required by protocol or by the ethics committee; annual safety report to ethics committee; final report to ethics committee
	Clinical trials with investigational medical devices (MD) - Only approval by ethics committee required (no Swissmedic approval required) - No mandatory trial specific insurance, but damages must be covered up to a maximum of CHF 3 million - Content of application dossier for IMD documentation: CE-label and instructions for use Safety reporting: reporting SAEs to Swissmedic only for new authorized IMDs (according to Art.15, Abs. 1 MepV); annual safety report to ethics committee
	Clinical trials with non-pharmacological/device interventions drugs - Approval by ethics committee required - No mandatory trial specific insurance, but damages must be covered up to a maximum of CHF 3 million - Safety reporting: no documentation of AEs; reporting fatal SAEs to ethics committee only if foreseen in the protocol or required by the ethics committee; reporting fatal SUSARS to ethics committee; annual safety report to ethics committee
Category B	**Clinical trials with investigational medicinal products (IMP)** - Approval by ethics committee and Swissmedic required - Compensation of damages: trial specific insurance mandatory; damages must be covered up to a maximum of CHF 10 million - Rules on IMP management: trial specific IMP management required, including IMP labelling and accountability - Content of application dossier for IMP documentation: summary of product characteristics and investigators brochure; GMP documentation required only for deviations in the manufacturing process and the composition of the IMP - Safety reporting: document AEs if required by protocol or by authorities; report SAEs with fatal outcome to ethics committee; annual safety report to ethics committee and Swissmedic; final report to ethics committee and Swissmedic
	Clinical trials with non-pharmacological/device interventions drugs - Compensation of damages: trial specific insurance mandatory; damages must be covered up to a maximum of CHF 10 million - Safety reporting: document AEs if written in the protocol or required by the ethics committee; report SAEs to ethics committee; report fatal SUSARS to ethics committee; annual safety report to ethics committee

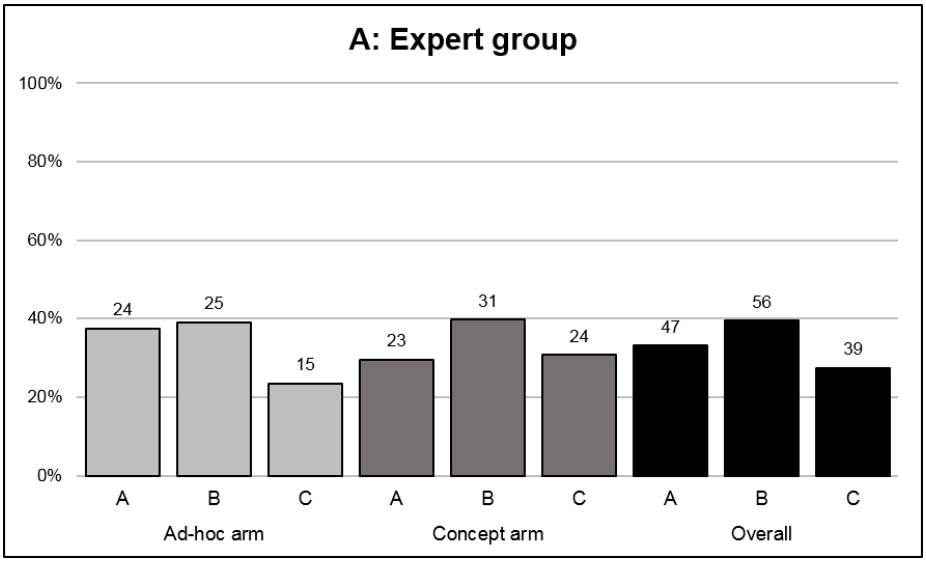
Category C	**Clinical trials with investigational medicinal products (IMP)** - Approval by ethics committee and Swissmedic required - Compensation for damages: trial specific insurance is mandatory and damages must be covered up to a maximum of CHF 10 millions - Rules on manufacturing and labelling of IMP: IMP management, including IMP labelling and accountability, is required - Content of application dossier on IMP documentation: investigators brochure; GMP documentation required - Safety reporting: documentation of AEs required; reporting of SAEs with fatal outcome to ethics committee; annual safety report to ethics committee and Swissmedic; final report to ethics committee and Swissmedic.
	Clinical trials with investigational medical devices (MD) - Approval by authorities (ethics committee and Swissmedic): approval by ethics committee and Swissmedic required - Compensation for damages: trial specific insurance is mandatory and damages must be covered up to a maximum of CHF 10 millions - Content of application dossier for IMD documentation: documentation of the quality and safety of the IMD required - Safety reporting: report SAEs to ethics committee and Swissmedic; annual safety report to ethics committee

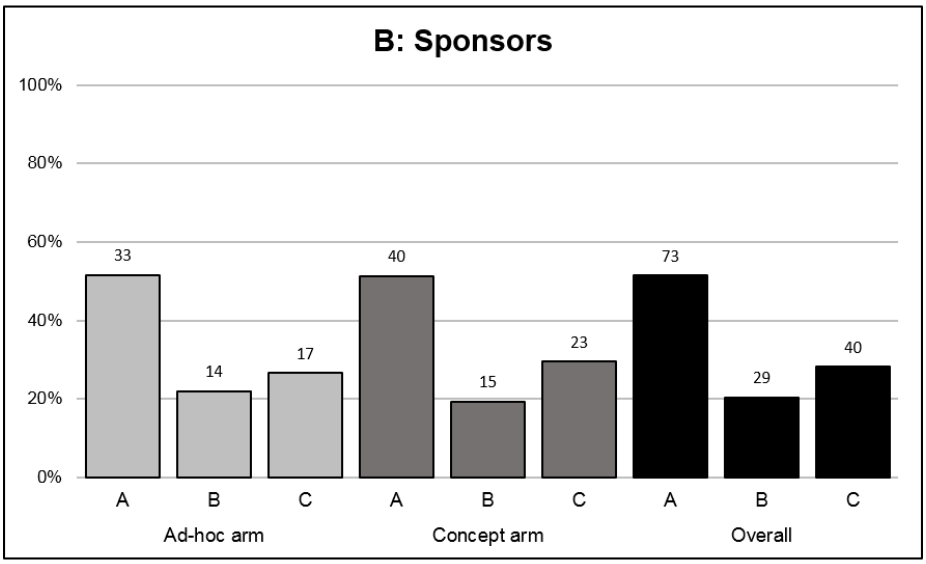
Web-appendix 4. Characteristics and reasons for exclusion of trial protocols

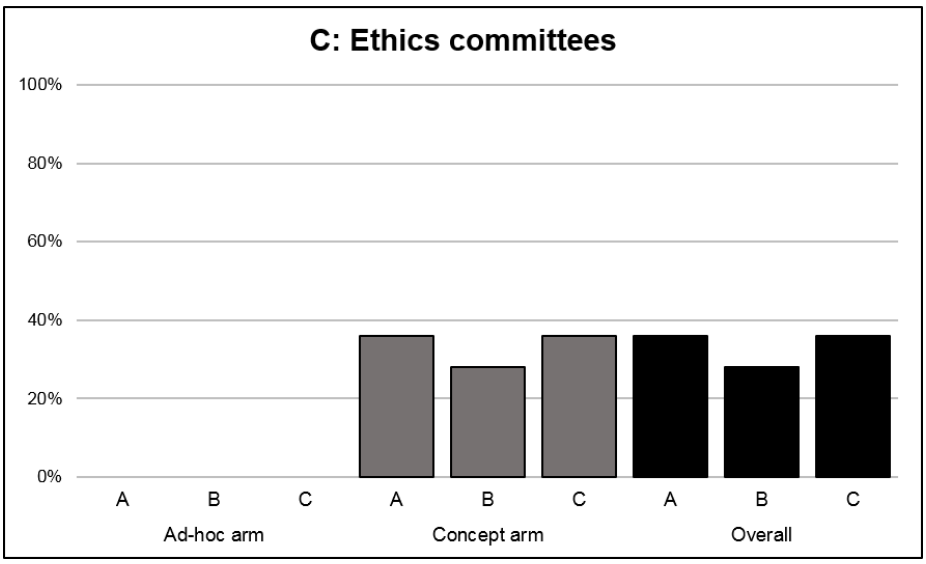
Reasons for exclusions	**n (%)**
Duplicate study protocol*	4 (4.4)
Non-responder	19 (21.1)
Withdrawal	3 (3.3)
Excluded by EG:	63 (71.1)
Total excluded	**89**
Reasons for exclusion by the EG	
Duplicated study protocol	3* (1.6) £
Duplicate sponsor	16* (28.1) £
Not clinical trial according to new definition	44 (70.3)
Not clinical trials according to the new definition by arm and affiliation	
Ad hoc	23 (35.9)+
Concept	21(28.6) +
Academy	39 (37.0) +
Industry	5 (14.7) +

* Multicentre trial protocol. The same protocol was provided by more than one ethics committee.
+ Not clinical trials, according to the definition in the new legislation.

Web-appendix 5. Distribution of categories by type of assessor







Web-appendix 6. Agreement between first and second expert group assessment

Comparison	**N**	**Observed agreement**	**Expected agreement**	**Kappa**	**95% Confidence interval**	p-value
All studies: risk categories	89	0.95	0.89	0.57	(0.300 to 0.800)	<0.001
All studies: study object categories	88	0.95	0.39	0.93	(0.841 to 0.982)	<0.001
Concept: risk categories	56	0.94	0.88	0.50	(0.153 to 0.808)	<0.001
Concept: study object categories	55	0.95	0.43	0.90	(0.773 to 1.000)	<0.001
Adhoc: risk categories	33	0.95	0.80	0.74	(0.357 to 0.960)	<0.001
adhoc: study object categories	33	0.97	0.37	0.95	(0.841 to 1.000)	<0.001